INSULIN THERAPY FOR CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

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Introduction

- Children and adolescents with type 1 diabetes
  - Regular monitoring of blood glucose.
  - Optimal diet.
  - Proper insulin therapy.
    - Dependent for survival.
    - No alternative treatment other than insulin.
    - Available for clinical use in the early 1920s.
Introduction

- Major advances in insulin therapy over the past 2 decades due to:
  - Self-monitoring of blood glucose in routine practice.
  - Change in philosophy of diabetes management: patient self-management, flexibility in lifestyle.
  - Insulin analogs: time-action profiles aligned with physiological insulin secretion.
History of insulin treatment

- Diabetes recognized as a distinct medical condition for at least 3500 yrs.

- Before the discovery of insulin, the only way to control diabetes was a diet low in CHO and high in fat and protein.

- In 1889, Minkowski removed the pancreas from a healthy dogs → developed the symptoms of diabetes → the relationship between pancreas and glucose metabolism.
History of insulin treatment

- In 1921, Banting and Best extracted insulin from the pancreas of cattle → injection to 3 yr-old boy with T1DM (1923 Novel Prize in medicine).

- In 1950s, the amino-acid structure of insulin was characterized by Frederick Sanger: A, B chain (51 A.A.) are bound together by disulfide bond (1958 Novel Prize in chemistry).
History of insulin treatment

- In 1977, the first genetically-engineered, synthetic "human" insulin by Herbert Boyer.
- In 1982, the first commercially available biosynthetic human insulin: Humulin®.
- In 1996, the first modified human insulin (insulin analogue): insulin lispro.
12/15/1922, 3yr, 5.8kg

2/15/1923, 4yr, 13kg
Types of insulin

- **1st phase: Conventional insulin**
  - beef/fork pancreas extract.

- **2nd phase: Recombinant human insulin**
  - Lesser antigenic effect and side effect.
  - Better subcutaneous absorption.
  - Lente, ultralente: combine zinc with regular human insulin.
  - NPH: addition of protamine to RI.

- **3rd phase: Insulin analogues**
  - Substitution or addition of amino acid residues.
  - Modify speed or length of action.
# Types of insulin

## TABLE 1. Pharmacokinetic properties of insulin

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>2–4 hrs</td>
<td>None</td>
<td>20–24 hrs</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1–3 hrs</td>
<td>6–8 hrs</td>
<td>18–22 hrs</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>2–4 hrs</td>
<td>4–10 hrs</td>
<td>10–18 hrs</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>0.5–1 hrs</td>
<td>2–3 hrs</td>
<td>5–8 hrs</td>
</tr>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td>5–15 min</td>
<td>0.5–2 hrs</td>
<td>3–5 hrs</td>
</tr>
<tr>
<td>Lispro Humalog</td>
<td>5–15 min</td>
<td>0.5–2 hrs</td>
<td>3–5 hrs</td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>5–15 min</td>
<td>0.5–2 hrs</td>
<td>3–5 hrs</td>
</tr>
<tr>
<td><strong>Premixed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% NPH/30% regular</td>
<td>0.5–1 hrs</td>
<td>3–12 hrs</td>
<td>10–16 hrs</td>
</tr>
<tr>
<td>50% NPH/50% regular</td>
<td>0.5–1 hrs</td>
<td>2–12 hrs</td>
<td>10–16 hrs</td>
</tr>
<tr>
<td>75% NPL/25% lispro</td>
<td>5–15 mins</td>
<td>1–4 hrs</td>
<td>10–16 hrs</td>
</tr>
<tr>
<td>50% NPL/50% lispro</td>
<td>5–15 mins</td>
<td>1–4 hrs</td>
<td>10–16 hrs</td>
</tr>
<tr>
<td>70% NPA/30% aspart</td>
<td>5–15 mins</td>
<td>1–4 hrs</td>
<td>10–16 hrs</td>
</tr>
</tbody>
</table>

NPH, neutral protamine hagedorn; NPL, neutral protamine lispro; NPA, neutral protamine aspart.
Regular insulin

- Hydrogen bond due to AA in C-terminal region of chain B → affinity for insulin molecule to self-aggregate into hexamer.

- Should be absorbed in monomer form for receptor binding.
Rapid-acting insulin analogs

- AA substitution in C-terminal of B chain.
- Absorbed more quickly, faster peak and shorter duration of action.
- Better postprandial glucose control.
- Decreased hypoglycemia.
- Given immediately before meals.
- More convenient for patients.
Insulin lispro (Humalog®)

- The first insulin analog for clinical use (1996).

- Switching proline and lysine at position 28 and 29 of chain B.

- Lower interaction $\rightarrow$ decreased hexamer formation $\rightarrow$ faster absorption $\rightarrow$ faster, higher and shorter peak of plasma insulin level.
Insulin lispro (Humalog®)

- With a complete coverage of basal insulin during 24 hrs, better glucose control, decreased hypoglycemia events.

- Superior for correction of incidental hyperglycemia control.

- Beneficial in ESRD and pregnant patients.
Insulin aspart (Novolog®)

- Substitution of proline by aspartic acid on position 28 of chain B.

- Similar pharmacokinetics to lispro.

- Better PPG control and less nocturnal hypoglycemia.

Insulin glulisine (Apidra®)

- Substitution of asparagaine by lysine on position 28 and lysine by glutamic acid on position 29 of chain B.
Mixtures of insulin analogs

- **NPL-Lispro-75/25 (Humalog Mix 25®)**
  - 75% lispro crystallized with protamine (NPL)-25% free lispro.
  - Humalog Mix 50®.

- **Aspart/crystallized aspart-protamine mixture-30**
  - NovoMix 30®.

- Easier use for the patient → a reduction of mistakes.
- Separated use: more logical, effective and less expensive.
Insulin glargine (Lantus®)

- The first long-acting insulin analog.
- Substitution of glycine for asparagine at position A21 and addition of two arginine to B30.
- Soluble at an acidic pH, less soluble at SC pH → forming of precipitation after injection → slower absorption.
- Peakless, lasts $22 \pm 4$ hrs.
- Cannot be mixed with other types of insulin.
Insulin detemir (Levemir®)

- Soluble without forming precipitate after injection.
- Removal of threonine at B30 and acylation of lysine at B29.
- Acylation → binding to albumin → half-life↑ and delayed entrance into cell → prolonged action and smaller peak of onset.
- Lasts 20 hrs.
- Cannot be mixed with other types of insulin.
Primary goal of insulin treatment

- Optimizing glycemic control.
- Reduce the development of microvascular and macrovascular complication.

➤ Reproduce physiologic insulin secretion: mimics endogenous insulin secretion.
Conventional insulin therapy

- 1-2 daily injections, combination of NPH and RI.
- Prebreakfast/ Predinner.
- NPH: basal and prandial insulin for lunch
- RI: prandial insulin for breakfast and dinner.
- Fewer injections → compliance.
- Does not mimic physiologic insulin secretion.
- Less flexibility with life-style and meal size.
Intensive insulin therapy

- Administration of insulin ≥ 3 times daily multiple daily injections (MDI) or pump.
- Basal dose: suppresses glucose production between meals and overnight.
- Bolus doses: 3 pre-meal doses, limit post-prandial hyperglycemia.
- More physiologic and lifestyle-flexibility.
- More injections
Conventional vs. Intensive therapy
( Diabetes Control and Complications Trial: DCCT)
Conventional vs. Intensive therapy
( Diabetes Control and Complications Trial: DCCT )
Analog-based basal-bolus regimen

- Glargine or detemir: basal insulin coverage.
- Rapid acting insulin: meal-related insulin.
- Reduction in fasting glucose, HbA1c and hypoglycemia.
- Lifestyle flexibility.
Analog-based basal-bolus regimen

Table 1. Changes in Glycemic Control after Lantus Therapy

<table>
<thead>
<tr>
<th></th>
<th>Before Lantus therapy</th>
<th>6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total insulin dose (unit/kg/day)</td>
<td>0.89±0.25</td>
<td>0.90±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Basal insulin dose (unit/kg/day)</td>
<td>0.57±0.16</td>
<td>0.50±0.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Meal time insulin dose (unit/kg/day)</td>
<td>0.33±0.14</td>
<td>0.41±0.14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.29±1.80</td>
<td>8.70±1.65</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total hypoglycemic events (/month)</td>
<td>15.1±15.5</td>
<td>7.6±8.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nocturnal hypoglycemic events (/month)</td>
<td>6.7±7.7</td>
<td>2.5±2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>220.7±163.8</td>
<td>177.7±79.8</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting C-peptide (ng/mL)</td>
<td>0.517±0.204</td>
<td>0.416±0.190</td>
<td>NS</td>
</tr>
</tbody>
</table>
Insulin pump

- In the late 1970s, self-monitoring of blood glucose and pump therapy were introduced.

- Battery powered, size of beeper.
- Reservoir to hold insulin, infusion set (tubing with a small plastic catheter)

- Rapid acting insulin: basal dose (50%) and bolus dose (50%).
Insulin pump

- Limited use in early pump: large size and difficulties in use of early pumps, psychological issues about wearing an external device, extra costs.

- Results of DCCT (1993)

- Improvement of devices: newer, smaller, safer and easier to use insulin pump.
  - Widespread use
CSII vs. MDI

- Contradictory results
  - Lacking control group, randomization, or crossover design.
  - Retrospective study

  - \(~1\) mmol/L ↓ in mean blood glucose, \(~0.5\)% ↓ in HbA1c and
  - \(~14\)% ↓ in insulin dose.
Advantages of insulin pump

- Most physiologic approach to insulin replacement.
- Decreased nocturnal hypoglycemia.
- Improved control of Dawn’s phenomenon.
- Lifestyle flexibility with variable exercise and meal.
disadvantages of insulin pump

- Infection at needle site.
- Limitations in rough sports or activities.
- More expensive than syringes used for insulin injection.
- Possibilities of insulin pump malfunctioning.
- DKA: pump battery is discharged, insulin reservoir runs empty, tubing becomes loose and insulin leaks, cannula becomes bent or kinked, preventing delivery → more frequent blood glucose monitoring.

Candidate should be carefully selected to assure adequate understanding of this therapeutic tool.
Indication for use of CSII in pediatrics
(Consensus statement from ESPE and LWPES)

Conditions under which CSII should be considered:
1. Recurrent severe hypoglycemia.
2. Wide fluctuations in blood glucose levels regardless of A1c.
3. Suboptimal diabetes control (i.e. A1c exceeds target range for age).
4. Microvascular complications and/or risk factors for macrovascular complications.
5. Good metabolic control but insulin regimen that compromises lifestyle.

Circumstances in which CSII might be beneficial:
1. Young children and especially infants and neonates.
2. Adolescents with eating disorders.
3. Children and adolescents with a pronounced dawn phenomenon.
5. Pregnant adolescents, ideally preconception.
7. Competitive athletes.
Non-invasive insulin delivery

- Inhaled insulin, oral, transdermal, intranasal, rectal, vaginal and ocular.
- Only now in development.
- Impermeability and low bioavailability
- Unpredictable insulin level
- Safety.
- Pulmonary delivery seems to be the most promising.
Inhaled insulin

- Lung: ideal route for administration of insulin.
  - Vast and well-perfused absorptive surface.
  - Lacks peptidases: escape from ‘first pass metabolism’.

Table 2. Insulin inhalation systems in current development

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Developer</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exubera</td>
<td>Nekar</td>
<td>Pfizer, Sanofi-Aventis</td>
</tr>
<tr>
<td>AERx® IDMS</td>
<td>Aradigm</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>Aerodose®</td>
<td>Aerogen</td>
<td>None</td>
</tr>
<tr>
<td>Spiros</td>
<td>Dura Pharmaceuticals</td>
<td>None</td>
</tr>
<tr>
<td>Technosphere</td>
<td>Pharmaceutica Discovery</td>
<td>annKind Corporation</td>
</tr>
<tr>
<td></td>
<td>Corporation</td>
<td></td>
</tr>
<tr>
<td>Microdose DPI</td>
<td>Microdose Technologies</td>
<td>Elan Corporation plc</td>
</tr>
<tr>
<td>AIRE</td>
<td>Alkermes</td>
<td>Eli Lilly</td>
</tr>
</tbody>
</table>
A variety of insulin delivery devices and system to lungs

- Liquid formulation: AERx (Novo Nordisk), dry powder system: Exubera (Pfizer).

Action after inhalation: 15 to 20 min.

Similar pharmacokinetic effect to rapid action insulin injection.

Non-invasive and painless rapid acting system.
Inhaled insulin

- Inhaled insulin before meals in conjunction with injected basal insulin → Reduced number of daily injections.
- No adverse pulmonary effects, but longer follow-up is required.
Oral insulin

- Advantage: mimic enterohepatic circulation of endogenous insulin.

- Low bioavailability (0.05%) and extensive degradation in gut mucosa.

- Hexyl-insulin monoconjugate 2 (HIM2)
  - Recombinant insulin with a small polyethylene glycol 7-hexyl group attached to B29 lysine.
  - Phase I/II clinical trials
  - Effective in controlling postprandial hyperglycemia.
## Oral insulin

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Developer</th>
<th>phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, Provalis (Macrulin)</td>
<td>Provalis</td>
<td>Phase II</td>
</tr>
<tr>
<td>Insulin, Oral Nobex (HIM-2)</td>
<td>Nobex (GSK)</td>
<td>Phase II</td>
</tr>
<tr>
<td>Insulin, Emisphere</td>
<td>Emisphere Technologies</td>
<td>Phase II</td>
</tr>
<tr>
<td>Insulin, Orasome (Endorex)</td>
<td>DOR BioPharma</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Insulin, oral Unigene</td>
<td>Unigene</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Insulin, BioSante, Oral</td>
<td>Biosante</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
Transdermal delivery

- Sonophoresis: low-frequency ultrasound → overcome impermeability of skin.
  - 1 hr of sonophoresis 3 times daily → 36 units delivered via transdermal patch.

- Iontophoresis: using a direct electric current.

- Lipid-based transferosomes: drug carrier based on phosphatidylcholine.
Conclusions

- At present insulin substitution therapy is still considered imperfect.
- Improved glycemic control can prevent diabetes complication.
- This requires early and prolonged implementation of intensive insulin therapy.
Conclusions

- The recent development of insulin analogs and insulin pump have allowed increased flexibility and more physiological management.

- MDI is more feasible option and CSII is useful only in some special situations.

- New non-invasive and painless route of administration are being developed. Inhaled insulin seems to be the most promising.
Conclusions

- Insulin regimen should always be tailored to each individual.
  - To maximize compliance and glycemic control.
  - To minimize hypoglycemia and weight gain.

- Everything is allowed as long as it is convenient and offers the best quality of life in combination with good metabolic control.